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The statements that follow are taken from the documents that were submitted by the applicant(s).

Petition for examination has been made in accordance with § 44 of the Patent Law.

[54] The use of substances having an aminergic effect to produce a drug for the treatment of viral infections of the central nervous system.

[57] The invention teaches the use of a substance from among the group of "dopaminergic neuropharmaceuticals, MAO-B inhibitors, D-methyl-selegiline, dopaminergic agonists and antagonists, adamantines, psycho-pharmaceuticals, neuroleptics" or mixtures thereof, that has an aminergic effect, for the purpose of producing a drug for the treatment of viral infections of target cells of the central nervous system. The quantity of substance within the drug that has an aminergic effect is adjusted with the proviso that the concentration of the substance that occurs within the target cells lies below a concentration limit that is defined by unaltered viral gene expression.

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Specification

The invention relates to a novel use of a substance from among the group of "dopaminergic neuropharmaceuticals, MAO-B inhibitors, D-methyl-selegiline, dopaminergic antagonists and agonists, adamantines, neuroleptics, psychopharmaceuticals" or mixtures thereof, that has an aminergic effect, for the purpose of producing a drug for the treatment of diseases of the central nervous system.

Aminergic substances are substances that intervene in the neural control of organs by means of biogenic amines. Accordingly, dopaminergic substances, for example, intervene with the neurotransmission that is governed by dopamine, a biogenic amine. MAO-B is one form of monoamine oxidase, which occurs, for the most part, in the so-called neuroglia cells of the central nervous system. Neuroglia cells form the supportive and sheathing tissue for the neurons, which constitute the actual nervous system. Included in the group of the neuroglia are the microglia (also called the Hortege cells), the mobile, smaller cells with the capacity for phagocytosis. To that degree, in the broader sense, microglia can be classified as part of the immune system. Agonists are ligands, often proteins or steroids, that can be bound to a receptor or transporter that is specific for the agonists, and thus trigger the subsequent biological reaction that is normal for the receptor-ligand complex. Agonists can be natural or artificial ligands. By contrast, antagonists also bond to receptors or transporters that are specific to the antagonists, such that, however, as a result of the receptor-ligand complex, the normal subsequent biological reaction is not triggered. To that degree, antagonists work as inhibitors for the normal subsequent biological reaction. Adamantines are substances that, in higher concentrations, promote the release of amines, especially dopamine, or rather, as a result of the inhibition of glutamatergic NMDA receptors, indirectly increase the dopaminergic tonus. Psychopharmaceuticals are substances that influence the function of the central nervous system. Included among these are antidepressants, tranquilizers, sleeping aids, and especially neuroleptics. Neuroleptics are drugs having an anti-psychotic, sedating and/or damping effect on the psycho-motor system. Included among the group of neuroleptics are, for example, tricyclic compounds from among the groups of the phenothiazines or thioxanthenes, such as promazine, thioridazine, levomepromazine, chlorpromazine, trifluopromazine, perphenazine, trifluoperazine, chlorprothixene and clopenthixol.

Included among diseases of the central nervous system are viral infections, especially retroviral infections of target cells of the central nervous system, especially of the microglia. Retroviruses are spherical, sheathed RNA viruses. Among the retroviral infections of the central nervous system, the lentiviruses HIV (Human Immunodeficiency Virus), SIV (Simian Immunodeficiency Virus), and the feline immunodeficiency virus, as well as neuro-virulent murine retroviruses play a particular role. In susceptible mice and rats, the latter cause a spongiform encephalopathy without an inflammatory component. Retroviral infections of target cells in the brain can, depending upon the replication kinetics of the virus, pursue an acute, sub-acute, or persistent course. The clinical picture of the retroviral infection frequently reflects the dynamics of pathogen proliferation and spread and the damage caused by the infection. From the pathological point of view, the

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retroviral infections are classified as inflammatory, degenerative, or a-pathogenic. According to the definitions determined here, diseases that are caused by so-called prions are classified as belonging to the group of diseases that are caused by viral infections. These are atypical, slow-acting pathogens, whose affinity to the group of viruses is currently being discussed. Included among the prions are pathogens that give rise to spongiform encephalopathies that can be transmitted (Creutzfeld-Jacob disease, for example).

Among viral infections, there is regularly a proliferation of the virus in question after the expression of viral genes in the target cell. The regulation of viral gene expression follows established molecular-biological principles such that, depending upon the type of virus and the nature of the infected cell, particular laws apply to the expression of viral genes. Fundamentally, the viral gene expression can be influenced by the administration of suitable substances, both in terms of enhancing or suppressing it insofar as the kinetics are concerned.

After a viral infection of target cells of the central nervous system, particularly with retro-viruses or pathogens of the aforementioned type, activation of the microglia, which, in contrast to the neurons, are still capable of proliferation, occurs. The consequences are histo-pathological damage of varying degrees in the brain, as well as neurological deficits. Of particular significance in all of this is the fact that the neurons that are damaged in the wake of the activation of the microglia, or neurons that lie in damaged areas of the brain themselves exhibit no indications of (retro)viral expression products. Therefore, the damaged neurons are deemed to be not infected. To that degree, the neurological deficits are merely an indirect consequence of the (retro) viral infection of the microglia. The involvement of cytokines (short-lived polypeptides that modulate the function of immune cells), neuro-transmitters and free radicals cannot be precluded.

From the state of the art, the use of a substance called selegiline, an MAO-B inhibitor, as a psychopharmaceutical agent, especially an antidepressant, is known (J. Knoll et al., Arch. Int. Pharmacodyn. Ther., 1965, 155, p. 154 ff.). Selegiline is the international, non-proprietary name for (R)-(-)-N-methyl-N-(1-phenyl-2-propyl)-2-propinyl amine. For example, in the literature citation E. Koutsilien et al., Europ. J. Pharmacol., 1996, 306, p. 181 ff, there is a description that for some time, selegiline has continued to be used as a drug for treating Parkinson's disease. For example, from the literature citation W.G. Tatton et al., Neurology, 1966, 47 (Suppl. 3), p. 171 ff., it is known, finally, that selegiline has also been used to treat Alzheimer's disease for some time as well. In the two latter-mentioned literature citations, results have been presented that show that selegiline can exhibit a neuro-protective effect, that is, that the administration of selegiline delays the apoptosis (cell death) of neurons – at least in the models of the aforementioned diseases. These studies, to be sure, do not pertain to neural damage that is caused, directly or indirectly, by viral infections. From the literature citation W.G. Tatton et al., Neurology, 1996, 47 (Suppl. 3), p. 171 ff, it is known, furthermore, that selegiline [sic—selegiline—Trans.] can influence the expression of the cell's own genes, such that the influence, depending upon the gene that is investigated (or rather the protein that is formed by it), is ambivalent, to be sure. Some proteins are

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formed to a greater degree, others are formed to a sub-normal degree, and the formation of other proteins still, is unaffected.

The invention's underlying technical problem is to provide a drug for the treatment of viral infections of target cells of the central nervous system.

This technical problem is resolved according to the invention by the use of a substance that has an aminergic effect from the group of "dopaminergic neuropharmaceuticals, MAO-B inhibitors, D-methyl-selegiline, dopaminergic agonists and antagonists, adamantines, psychopharmaceuticals, neuroleptics" or mixtures of them, for the purpose of producing a drug for the treatment of viral infections of target cells of the central nervous system, such that the quantity of the aminergically active substance in the drug is adjusted with the proviso that the concentration of the substance that occurs within target cells lies below a concentration limit defined by unaltered viral gene expression. — The corresponding adjustment to the concentration of the substance can be easily undertaken via the dose by considering the galenic form of administration that has been chosen. A corresponding dose limit of the substance that has been administered is correlated at all times with the concentration limit within the target cells. The dose limit, and consequently, the concentration limit, in other words, is defined by virtue of the fact that the kinetics of the viral gene expression, when the substance is administered within the dose limit, is approximately equal to the viral gene expression without the administration of the substance. The dose limit that is assigned to an individual substance for a particular viral infection can easily be determined by trials, in animal experimentation models, for example, or in cell cultures, such as neural or glial cell cultures.

The invention is based, first of all, upon the recognition that aminergically active substances also exert an influence upon the expression of viral genes in the target cells and thus, can control the proliferation of the viruses. Thus, a pharmaco-virological interaction in the target cells results. This, in itself is surprising, because the fact that is known from the literature citation [by] W.G. Tatton et al., Neurology, 1996, 47 (Suppl. 3), p. 171 ff., that the expression of a few of the cell's own genes into uninfected cells can be influenced, does not permit the conclusion that the expression of viral genes into the target cells can be influenced by the substances in question. As a result of the infection of a target cell with a virus, in point of fact, the normal gene expression into the target cell is altered to a considerable degree, or rather, disturbed, in favor of the expression of viral genes. Of particular significance for the invention, however, is the surprising recognition that the effect of the substance in question upon the viral gene expression depends upon the dose of the substance. In the case of the substances that were studied, namely, it was found that high doses led to no decrease of viral gene expression, but rather, to an increase of the viral gene expression, whereas comparatively low doses decrease the viral gene expression, which is, ultimately, therapeutically desired. To be sure, the possibility cannot be precluded that these dose-dependent pharmaco-virological interactions can, in the case of certain substances, be shifted in the reverse direction as well.

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In a preferred embodiment form of the invention, the aminergic substance is an MAO-B inhibitor, especially selegiline. The use according to the invention is particularly well suited to the treatment of retroviral infections of target cells of the central nervous system, the microglia, for example, with retroviruses from among the group of "lentiviruses such as HIV and SIV, feline immunodeficiency virus, neuro-virulent murine retroviruses."

In a preferred embodiment form of the invention, the drug is galenically prepared for intra-peritoneal or subcutaneous injection. This is to good purpose, especially in the case of selegiline, because in the gastro-intestinal tract, selegiline is absorbed quite quickly and, among other things, it is metabolized to amphetamine. Consequently, in the case of oral administration of the drug, the adjustment of the selegiline concentration in the target cells would be more difficult via the dose, and in addition, possibly dependent upon individual variations of metabolizing in the area of the gastro-intestinal tract. To the extent that metabolizing in the area of the gastro-intestinal tract is considered and a sufficiently great distance is selected from the dosage limit or the concentration limit of selegiline, however, even an oral form of administration can be realized.

A particularly preferred embodiment form of the invention is characterized by the fact that the aminergically active substance is selegiline and the quantity of selegiline in the drug is adjusted with the proviso that the dose of the aminergically active substance lies beneath 0.5 mg/kg, preferably beneath 0.1 mg/kg, most preferably beneath 0.05 mg/kg, or even beneath 0.01 mg/kg. Concentrations in the target cells that correspond to these values lie within the ranges beneath ca. 10^{-9} M, preferably beneath 10^{-10} M, or most preferably, beneath 10^{-11} M.¹

In what follows, the invention will be elucidated in greater detail by virtue of examples.

A rat model was used in all examples. For this purpose, rats were infected neonatally with neuro-virulent retroviruses. The viruses used were high-grade microgliotropic murine retroviruses (MuLV²). Thus, microglia are the target cells. In this animal model, after a defined incubation period, a spongiform encephalopathy develops, the extent of which follows an anatomically established principle. The occurrence of clinical symptoms of a neurological disease over time, in the absence and presence of an MAO-B inhibitor was studied, as well as its dose dependence.

Example 1

In Fig. 1, data are shown that depict the proportion of rats that contracted the disease spongiform encephalopathy, expressed as a percentage, in individual groups, depending upon the time that had elapsed following infection. The solid rhombi stand for a group of 73 rats that were not treated. This group thus represents the control group. The solid squares stand for a group of 25 rats that received injections of 1.0 mg of

¹ Presumably mole.—Trans

² Murine leukemia virus.—Trans.

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selegiline/kg of body weight, intraperitoneally, on the 13th day following infection. The open squares stand for a group of 6 rats that received 0.05 mg of selegiline/kg of body weight, injected intraperitoneally three times (on the 15th, 22nd, and 30th day after infection). The open triangles stand for a group of 7 rats that received 0.05 mg of selegiline/kg of body weight, 1 time, injected intraperitoneally.

By means of a comparative observation of the curves³ with the solid symbols, one can recognize that the dosage limit for selegiline lies at ca. 1.0 mg of selegiline/kg of body weight, since the curve that was assigned to this selegiline dose nearly identically covers the curve of the control group and consequently, this dose of selegiline exerts no distinct influence upon the incubation period. By contrast, the two curves that are allocated to selegiline doses beneath 1.0 mg selegiline/kg of body weight are clearly beneath the curve for the control group, which verifies the lengthening of the incubation period and thus, the desired delay of the disease. In addition, the percentage of animals that contracted the disease is markedly reduced in the groups that were treated with the lower dose.

Example 2

In Fig. 2, data are shown in a manner that corresponds to Example 1. The solid circles stand for the group of 73 rats that was not treated. The open triangles stand for a group of 25 rats that received 1.0 mg of selegiline/kg of body weight by means of intraperitoneal injection, but not until the 17th day following infection.

By means of a comparative observation of the two curves, one recognizes that the dosage limit of selegiline that was administered later, compared to Example 1, even led to a shortening of the incubation period. By these means, it is proven, on the one hand that only the administration of a dose that is clearly below the dosage limit gives rise to the desired increase of the incubation period, and, on the other hand, that the effect shown in Example 1 does not merely result from the fact that the administration of the low selegiline doses took place 1 or 2 days later than the administration of the dosage limit for selegiline.

Example 3

In additional experiments with substances other than selegiline that provide orientation, work proceeded in accordance with Example 2. At issue here were MAO-B inhibitors that were not metabolized to amphetamine. Qualitatively, the results (not shown) corresponded to those from Fig. 2. Thus, proof is furnished, first of all, that even MAO-B inhibitors, which cannot be metabolized to amphetamine, exhibits [sic] a corresponding pharmaco-virological interaction in infections of the microglia with MuLV or NT40.⁴ Furthermore, the dosage limit in the case of such MAO-B inhibitors, which cannot be metabolized to amphetamine, is also presumably within a range of 1 mg/kg of body weight, or less. This trial also proves, however, that the pharmaco-virological

³ I received no drawings—Trans.

⁴ Expansion uncertain —Trans

effect that occurs in the case of selegiline is not merely based upon amphetamine that might possibly form.

In accompanying trials, it was finally verified that the length of the incubation period depends, in point of fact, upon the virus titer and the number of infected microglia cells in the brain. This occurred with the help of in situ hybridizing. It was shown that an alteration of the incubation period is correlated with an increase or decrease of the content of viral transcripts in the target cells in question. By these means, it is proven that with selegiline, in point of fact, influencing of viral gene expression occurs.

The results shown above can be transferred to human medical purposes with respect to the dosage limit or the limit of concentration in the target cells, respectively if, as a result of a comparison with substances already used (for other purposes) in the usual way for the profession, consideration is given to the degree to which the species-specific absorption and transport of the active ingredient in human beings is distinct from the corresponding behavior of the active substance in the animal model. In the case of human beings, therefore, the dosage limit that is allocated to the concentration limit could, in any case, lie above 0.1 mg/kg of body weight, due to the fact that in the case of human beings, in contrast to rats, as a rule, comparatively somewhat smaller doses are needed for comparable physiological effects. This is a dose that corresponds with a concentration of selegiline that is clearly below (on an order of magnitude of ca. 1/100) any limit of concentration for MAO-B inhibition. As a matter of principle, a drug that is produced in accordance with the invention is naturally suited to both purposes having to do with human as well as veterinary medicine, such that in each case, then, in the manner indicated, consideration must be given to adjusted doses.

With respect to the way in which the aminergic substances, especially selegiline, function, it is assumed that the pharmaco-virological effect occurs either directly, by way of interference with the viral transcription, or by influencing the target cells by way of mechanisms that have been unknown thus far.

Patent Claims

1. The use of a substance from among the group of "dopaminergic neuropharmaceuticals, MAO-B inhibitors, D-methyl-selegiline, dopaminergic agonists and antagonists, adamantines, psycho-pharmaceuticals, neuroleptics" or mixtures thereof, that has an aminergic effect, for the purpose of producing a drug for the treatment of viral infections of target cells of the central nervous system, such that the amount of the substance having the aminergic effect in the drug is adjusted with the proviso that the concentration of the substance that occurs in the target cells lies below a concentration limit that is defined by unchanged viral gene expression.
2. The use according to claim 1, such that the aminergically active substance is an MAO-B inhibitor, preferably selegiline.

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3. The use, according to claim 1 or 2, for the treatment of retroviral infections of target cells of the central nervous system with retroviruses from among the group of "lentiviruses such as HIV and SIV, feline immunodeficiency virus, neurovirulent murine retroviruses."
4. The use, according to one of the claims 1 through 3 for the treatment of viral infections of the microglia.
5. The use, according to one of the claims 1 through 4, whereby the drug is prepared galenically for the purpose of intraperitoneal or subcutaneous injection.
6. The use, according to one of the claims 1 through 5, in which the substance having the aminergic effect is selegiline and the quantity of selegiline in the drug is adjusted with the proviso that the dose of the aminergically active substance lies beneath 0.5 mg/kg, preferably beneath 0.05 mg/kg, and most preferably, beneath 0.01 mg/kg.

Enclosed 1 page(s) of drawings

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